

The clinical efficacy of triclosan/copolymer and other common therapeutic approaches to periodontal health

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ABSTRACT

The maintenance of an effective level of oral hygiene is the cornerstone of all attempts to prevent and control periodontal disease, and yet the widespread prevalence of the disease indicates the inability of most people to maintain a level of plaque control commensurate with periodontal health. The inclusion of antibacterial agents, such as chlorhexidine and triclosan, in oral care products has provided a means to improve oral health. Randomised, controlled clinical trials have demonstrated that the unsupervised use of a dentifrice (toothpaste) containing triclosan/copolymer significantly improves gingival health, prevents the onset of periodontitis and reduces further progression of tissue destruction. The delivery of such benefits has positive implications for the oral health of individuals and populations.

Keywords Oral care products, periodontal disease, triclosan

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INTRODUCTION

The inflammation causing periodontal diseases is initiated by bacterial biofilms (dental plaque) that form on the surfaces of teeth in close proximity to the supporting tissues of the teeth. Initially, the biofilms develop above (Fig. 1a) the gum margin (supragingival) but, in the absence of effective oral hygiene, will inevitably extend below (Fig. 1b) the gum margin (subgingival). The inflammatory and immune responses to these biofilms are primarily responsible for the subsequent destruction of the periodontal tissues. The most common forms of periodontal disease are gingivitis and periodontitis. The term gingivitis denotes a lesion that is confined to the gingiva (gum) and is reversible, provided that the individual maintains an effective level of plaque control. However, gingivitis is the precursor of periodontitis, which is caused by the apical spread of inflammation, and the irreversible loss of tooth support. Gingivitis and periodontitis are a continuum, and

although the susceptibility of an individual to periodontitis is influenced by many factors, such as smoking, diabetes and genetics, the weight of evidence indicates that the prevention of gingival inflammation prevents periodontitis [1].

Periodontal diseases are prevalent in populations around the world [2]. More than 82% of US adolescents have overt gingival inflammation [2], and in Western Europe 36% of those aged 35–44 years have moderate periodontitis and approximately 10% have severe periodontitis [3]. The prevalence and severity of periodontitis increases with age [4] and, as the increasingly numerous elderly population retain more of their teeth into later life, periodontal disease will pose an increasing threat to their natural dentition and, potentially, their general health.

Although many factors influence the susceptibility of an individual to periodontitis, the process of tissue destruction is initiated by plaque bacteria. The cornerstone of any attempt to prevent and control periodontal disease is the maintenance of an effective level of plaque control by the individual at home, and available evidence indicates that most people find it difficult to maintain this level. In the UK, for example, 74% of adults claimed to brush their teeth twice a day, and yet 72% of 25–34-year-olds had visible plaque on 30% of teeth, and those aged 65 years and over

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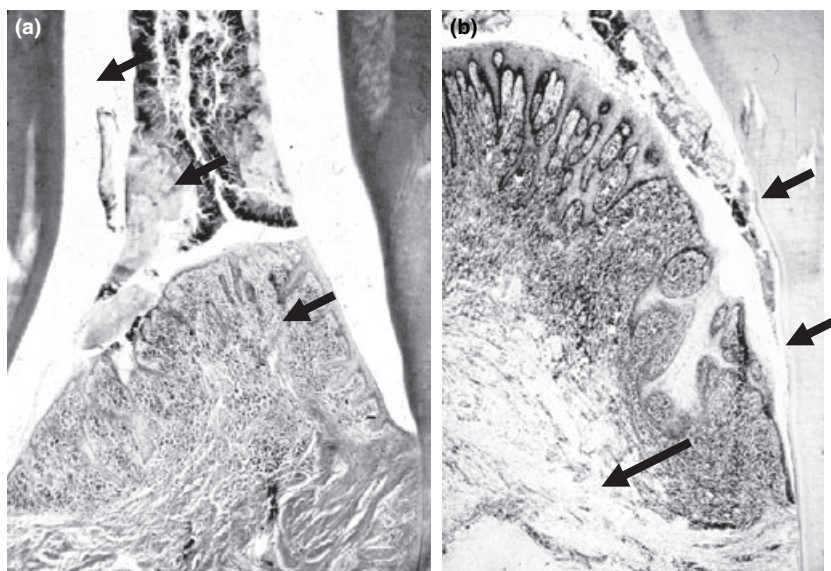


Fig. 1. Supragingival plaque and gingival inflammation (a). Subgingival plaque and irreversible loss of tooth support (b).

had visible plaque on 44% of teeth [4]. It was thus concluded that there is a need to improve the oral cleanliness of the majority of the population if periodontal health is to be improved.

Conventional dentifrices (toothpastes) are complex mixtures of abrasives, surfactants and humectants that enhance the physical removal of plaque bacteria from the tooth surfaces. The principle and benefits of adding chemical agents to dentifrices is exemplified by the inclusion of fluoride, which has been a major factor in reducing the prevalence of dental caries worldwide [5]. Given the importance of plaque bacteria in initiating periodontal disease, the incorporation of an antibacterial agent into oral care products would appear to be a logical development. This review will consider clinical studies, of at least 6 months' duration, that have assessed the effectiveness of agents in improving plaque control and periodontal disease.

DENTIFRICES

Stannous fluoride

Although launched initially in the 1950s to deliver the anti-caries benefit of fluoride, dentifrices containing stannous fluoride also exhibit intrinsic antimicrobial effects [6]. Stabilised stannous fluoride dentifrices improve gingival health as compared with a conventional dentifrice, but this has not always been accompanied by a significant reduction in plaque [7,8].

Triclosan

Triclosan is a broad-spectrum antibacterial agent with a good safety record as used in many consumer products, e.g., deodorants and soaps. The fact that triclosan is a non-ionic molecule allows it to be formulated in conventional dentifrices, but it does not bind to the oral surfaces for more than a few hours and therefore does not deliver a sustained level of anti-plaque activity. Two attempts have been made to overcome this problem.

Triclosan/copolymer

The first approach was to add a copolymer, polyvinylmethyl ether maleic acid, which increased the uptake of triclosan and its retention [6] on oral surfaces (plaque, teeth and mucosa). Subsequent studies have demonstrated that triclosan/copolymer dentifrices containing 0.3% triclosan, 2.0% copolymer and fluoride (1100/1450 p.p.m. F) (Colgate Total, Colgate-Palmolive company, NJ, USA) maintain concentrations of triclosan in plaque that exceed the MIC values of many plaque bacteria for up to 12 h [9].

The efficacy of this triclosan/copolymer dentifrice in reducing plaque and improving gingival health has been assessed in numerous randomised, controlled clinical trials, and the results have been summarised in a number of traditional and systematic reviews [10,11]. The participants in all studies were adults with plaque and gingivitis

[11]. Participants were randomly allocated to use either the triclosan/copolymer dentifrice or a conventional fluoride dentifrice for 6 months. They were given no oral hygiene instruction and were simply asked to use their allocated dentifrice twice a day. With the exception of one trial, all dentifrices were supplied in plain white tubes.

The meta-analyses of data from 16 studies demonstrated that the triclosan/copolymer dentifrice was significantly more effective in improving plaque control and gingival health than a fluoride dentifrice. The weighted mean difference (WMD) of -0.48 for the Quigley–Hein Plaque Index corresponds to a 23% reduction in plaque when compared with a fluoride dentifrice. The WMD of -0.15 for heavy plaque deposits corresponds to a 15% reduction. In relative terms, there was a 49% reduction in the proportion of sites that had heavy plaque. The WMD of -0.26 for gingival inflammation corresponds to a 23% reduction. The WMD of -0.34 for gingival bleeding corresponds to a 12% reduction which, in relative terms, corresponds to a 49% reduction in the proportion of sites with bleeding.

The progression of gingivitis to periodontitis is an unpredictable event, but bleeding sites are more likely to progress to periodontitis than non-bleeding sites [12]. Since the triclosan/copolymer dentifrice significantly reduced gingival bleeding, further studies have assessed whether the dentifrice could also have beneficial effects on periodontitis. A 3-year randomised clinical trial involving adolescents who were at risk of developing early periodontitis demonstrated that the triclosan/copolymer dentifrice was indeed significantly more effective than a standard fluoride toothpaste in preventing the onset of periodontitis [13]. After 3 years, the triclosan/copolymer dentifrice reduced the amount of attachment loss (early periodontitis) per subject by 50% and the number of affected sites by 41%. In another 3-year study, which involved patients who already had periodontitis, the triclosan/copolymer dentifrice was significantly more effective than a fluoride dentifrice in reducing pocket depth and further attachment loss [14]. Data from a 5-year clinical trial in Australia demonstrated that the triclosan/copolymer dentifrice could slow the progression of disease in a normal adult population [15]. Finally, the triclosan/copolymer dentifrice significantly improved the gingival health and

periodontal status in smokers when compared with a standard fluoride dentifrice [16].

No adverse events have been reported in any of the studies, and no shifts in the microflora of supragingival plaque favouring the growth of either opportunistic or pathogenic bacterial or yeast species have been observed [17,18].

Initially, the benefits of triclosan/copolymer dentifrice were attributed solely to the antibacterial activity of triclosan, but several studies have demonstrated that triclosan may also exert a significant anti-inflammatory effect. Triclosan reduces skin and mucosal inflammation [19,20], and there is clinical evidence that this may also occur in the gingiva [21]. Further in-vitro studies have demonstrated that triclosan reduces the production of prostaglandin E_2 by cells stimulated with either interleukin- 1β or tumour necrosis factor- α [22], and the production of interleukin- 1β by fibroblasts stimulated by tumour necrosis factor- α [23]. More recently, it has been reported that triclosan reduces microsomal prostaglandin E synthase-1 expression in human gingival fibroblasts [24].

Triclosan/zinc citrate

The second approach to overcoming the lack of substantivity and efficacy of triclosan has been to combine triclosan with zinc citrate, the latter having been shown to be substantive and to inhibit plaque and gingivitis [25]. Several clinical studies of at least 6 months' duration have shown that dentifrices containing zinc citrate and triclosan are significantly more effective than a fluoride dentifrice in controlling plaque and gingivitis [26].

MOUTH RINSES

Chlorhexidine

Chlorhexidine digluconate is the most powerful anti-plaque agent available. Since 1970, numerous clinical trials have demonstrated its effectiveness in improving plaque control and gingival health when used as an adjunct to toothbrushing [27]. Its effectiveness is attributed to the dicationic nature of chlorhexidine, which ensures its reversible binding with the negatively charged molecules in the oral cavity, so that activity persists for several hours after application. However, its

long-term use is precluded because of its propensity to stain the teeth, which is the result of interactions between chlorhexidine on the tooth surfaces and tannins in the diet.

Triclosan/copolymer

Three clinical trials of 6 months' duration have assessed the effectiveness of a mouthrinse containing triclosan/copolymer [28]. Reductions in plaque and gingivitis ranged from 24% to 36% and from 19% to 23%, respectively, when compared with a placebo rinse.

Cetylpyridinium chloride

Mouthrinses containing the cationic surface-active agent cetylpyridinium chloride have been marketed since 1940. When used as an adjunct to toothbrushing, the rinse significantly reduced plaque and gingivitis by 28% and gingival bleeding by 67%, respectively [29].

Essential oils

A combination of thymol and eucalyptol, together with menthol and methylsalicylate in a hydroalcohol vehicle (Listerine, Johnson & Johnson, Raritan, NJ, USA), is also used. Several clinical trials [30,31] have demonstrated that when used as an adjunct, this antiseptic mouthwash provides significant benefits, with up to 56% reductions in plaque and 35% reductions in gingivitis. However, in general, it has been found to be less effective than chlorhexidine.

Amine fluoride/stannous fluoride

Although clinical studies of short duration have generally shown an amine fluoride/stannous fluoride rinse to improve plaque control and gingival health [32], these benefits have not been consistently demonstrated in long-term studies. In a clinical study of 7 months' duration, an amine fluoride/stannous fluoride rinse reduced plaque by 5% and gingival bleeding by 30% when compared with a placebo rinse, but no benefit to gingival health has been observed [33]. In 1996, it was reported that a combination of amine/stannous fluoride dentifrice and amine/stannous fluoride mouthrinse was no more effective than a conventional fluoride dentifrice and

rinse in improving plaque control and gingival health. Subsequent studies have reported that the combination of amine/stannous fluoride dentifrice and rinse significantly reduced plaque by 25% and 16% [33] but failed to deliver gingival benefits when compared with a conventional fluoride dentifrice and mouthrinse.

CONCLUSION

The need for effective control of dental plaque has led to a large number of clinical studies with antibacterial agents in oral hygiene formulations. Antibacterial agents have been shown to vary in their effectiveness in improving plaque control and gingival health when compared to a conventional fluoride dentifrice in studies of at least 6 months' duration. The unsupervised use of a dentifrice containing triclosan/copolymer has been shown to prevent the onset and progression of periodontitis for at least 3 years. Such improvements in periodontal health could have beneficial effects on systemic health.

REFERENCES

1. Kinane DF, Attstrom R. Advances in the pathogenesis of periodontitis. Consensus Report. *J Clin Periodontol* 2005; **32** (suppl 6): 130–131.
2. Albandar JM, Rams TE. Global epidemiology of periodontal diseases: an overview. *Periodontology* 2000, 2002; **29**: 7–10.
3. Sheiham A, Netuveli GS. Periodontal diseases in Europe. *Periodontology* 2000, 2002; **29**: 104–121.
4. Morris AJ, Steele J, White DA. The oral cleanliness and periodontal health of UK adults in 1998. *Br Dent J* 2001; **191**: 186–192.
5. Bratthall D, Hansel-Petersson G, Sundberg H. Reasons for the caries decline: what do the experts think? *Eur J Oral Sci* 1996; **104**: 416–422.
6. Tinanoff N. Review of the antimicrobial action of stannous fluoride. *J Clin Dent* 1990; **2**: 22–27.
7. Beiswanger BB, McClanahan SF, Bartizek RD, Lanzalaco AC, Bacca LA, White DJ. The comparative efficacy of stabilized stannous fluoride dentifrice, peroxide/baking soda dentifrice and essential oil mouthrinse for the prevention of gingivitis. *J Clin Dent* 1997; **8**: 46–53.
8. Mankodi S, Bartizek RD, Winston LL, Biesbrock AR, McClanahan SF, Tao H. Anti-gingivitis efficacy of a stabilized 0.454% stannous fluoride/sodium hexametaphosphate dentifrice. A controlled 6-month clinical trial. *J Clin Periodontol* 2005; **32**: 75–80.
9. Volpe AR, Petrone ME, DeVizio W, Davies RM, Proskin HM. A review of plaque, gingivitis, calculus and caries clinical efficacy studies with a fluoride dentifrice containing triclosan and PVM/MA copolymer. *J Clin Dent* 1996; **7** (suppl): S1–S14.

10. Davies RM, Ellwood RP, Davies GM. The effectiveness of a toothpaste containing Triclosan and polyvinyl-methyl ether maleic acid copolymer in improving plaque control and gingival health. A systematic review. *J Clin Periodontol* 2004; **31**: 1029–1033.
11. Gunsolley JC. A meta-analysis of six-month studies of antiplaque and antigingivitis agents. *J Am Dent Assoc* 2006; **137**: 1649–1657.
12. Lang N, Joss A, Orsanic T, Gusberti FA, Siegrist BE. Bleeding on probing. A predictor for the progression of periodontal disease? *J Clin Periodontol* 1986; **13**: 590–596.
13. Ellwood RP, Worthington HV, Blinkhorn AS, Volpe AR, Davies RM. Effect of a triclosan/copolymer dentifrice on the incidence of periodontal attachment loss in adolescents. *J Clin Periodontol* 1998; **25**: 363–367.
14. Rosling B, Wannfors B, Volpe AR, Furuichi Y, Ramberg P, Lindhe J. The use of a triclosan/copolymer dentifrice may retard the progression of periodontitis. *J Clin Periodontol* 1997; **24**: 873–880.
15. Cullinan MP, Westerman B, Hamlet SM, Faddy MJ, Seymour GJ. The effect of a triclosan containing dentifrice on the progression of periodontal disease in an adult population. *J Clin Periodontol* 2003; **30**: 414–419.
16. Kerdvongbundit V, Wikesjo UME. Effect of triclosan on healing following non-surgical periodontal therapy in smokers. *J Clin Periodontol* 2003; **30**: 1024–1030.
17. Zambon JJ, Reynolds HS, Dunford RG *et al.* Microbial alterations in supragingival dental plaque in response to a triclosan-containing dentifrice. *Oral Microbiol Immunol* 1994; **10**: 247–255.
18. Cullinan MP, Hamlet SM, Westerman B, Palmer JE, Faddy MJ, Seymour GJ. Acquisition and loss of *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans* and *Prevotella intermedia* over a 5-year period: effect of a triclosan copolymer dentifrice. *J Clin Periodontol* 2003; **30**: 532–541.
19. Kjaerheim V, Barkvoll P, Waaler SM, Rolla G. Triclosan inhibits histamine-induced inflammation in human skin. *J Clin Periodontol* 1995; **22**: 423–426.
20. Barkvoll P, Rolla G. Triclosan reduces the clinical symptoms of the allergic patch test reaction (APR) elicited with 1% nickel sulphate in sensitised patients. *J Clin Periodontol* 1995; **22**: 485–487.
21. Ramberg P, Furuichi Y, Sherl D *et al.* The effect of triclosan on developing gingivitis. *J Clin Periodontol* 1995; **22**: 442–448.
22. Modeer T, Bengtsson A, Rolla G. Triclosan reduces prostaglandin biosynthesis in human gingival fibroblasts challenged with interleukin-1 in vitro. *J Clin Periodontol* 1996; **23**: 927–933.
23. Mustafa M, Wondimu B, Ibrahim M, Modeer T. Effect of triclosan on interleukin-1 β production in human gingival fibroblasts challenged with tumor necrosis factor α . *Eur J Oral Sci* 1998; **106**: 637–643.
24. Mustafa M, Wondimu B, Yucel Lindberg T *et al.* Triclosan reduces microsomal prostaglandin E synthase-1 expression in human gingival fibroblasts. *J Clin Periodontol* 2005; **32**: 6–11.
25. Williams C, McBride S, Mostler K *et al.* Efficacy of a dentifrice containing zinc citrate for the control of plaque and gingivitis: a six-month clinical study in adults. *Comp Cont Educ Dent* 1998; **19** (Special Issue): 4–15.
26. Svaton B, Saxton CA, Huntington E, Cummins D. The effects of three silica dentifrices containing triclosan on supragingival plaque and calculus formation and on gingivitis. *Int Dent J* 1993; **43** (suppl 1): 75–81.
27. Jones CG. Chlorhexidine: is it still the gold standard? *Periodontology* 2000, 1997; **15**: 55–62.
28. Ayad F, Berta R, Petrone M, DeVizio W, Volpe AR. Effect on plaque removal and gingivitis of a triclosan-copolymer pre-brush rinse: a six-month clinical study in Canada. *J Can Dent Assoc* 1995; **61**: 59–61.
29. Allen DR, Davies RM, Bradshaw B *et al.* Efficacy of a mouthrinse containing 0.05% cetylpyridinium chloride for the control of plaque and gingivitis: a six month clinical study in adults. *Comp Cont Educ Dent* 1998; **19** (Special Issue): 20–26.
30. Grossman E, Meckel AH, Isaacs RL *et al.* A clinical comparison of antibacterial mouthrinses: effects of chlorhexidine, phenolics and sanguinarine on dental plaque and gingivitis. *J Periodontol* 1989; **60**: 435–440.
31. Charles CH, Mostler KM, Bartels LL, Mankodi SM. Comparative antiplaque and antigingivitis effectiveness of a chlorhexidine and an essential oil mouthrinse: 6-month clinical trial. *J Clin Periodontol* 2004; **31**: 878–884.
32. Guarnelli ME, Zangari F, Manfrini R, Scapoli C, Trombelli L. Evaluation of additional amine fluoride/stannous fluoride containing mouthrinse during supportive therapy in patients with generalized aggressive periodontitis. *J Clin Periodontol* 2004; **31**: 742–748.
33. Paraskevas S, Versteeg PA, Timmerman MF, Van der Velden U, Van der Weijden GA. The effect of a dentifrice and mouth rinse combination containing amine fluoride/stannous fluoride on plaque and gingivitis: a 6-month field study. *J Clin Periodontol* 2005; **32**: 757–764.